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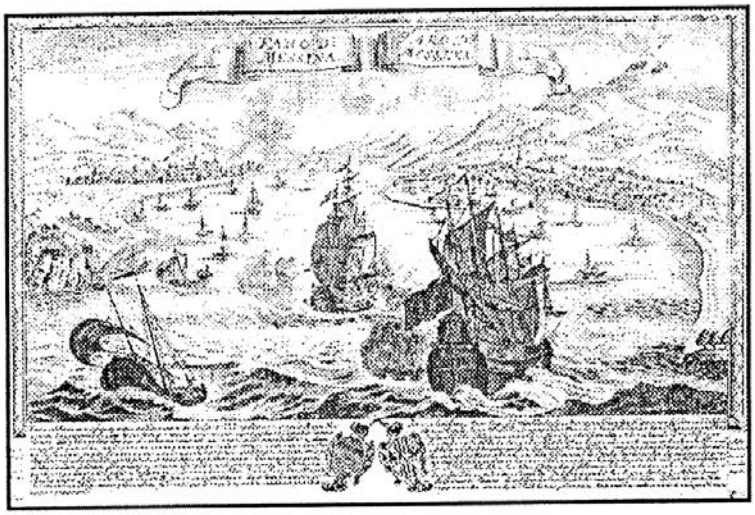
Classe I di Scienze Fisiche
Matematiche e Naturali

WORKSHOP ON PLATINUM CHEMISTRY

ABSTRACTS



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INTERSTRAND DNA ADDUCTS OF PLATINUM COMPLEXES

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Numerous studies suggest that the antitumor action of platinum drugs is related to its ability to react with cellular DNA. The platinum drugs bind to DNA preferentially to guanine residues at the N(7) position, producing monofunctional adducts that can subsequently close to bifunctional lesions. Most of the structural information currently available pertains to the intrastrand cross-links of platinum between adjacent purines. 90% of these adducts are formed in the reaction of linear double stranded DNA with *cis*-diaminedichloroplatinum (II) (cisplatin), which is one of the most effective anticancer drugs. Its minor DNA adducts are monofunctional lesions, interstrand cross-links and intrastrand cross-links between two nonadjacent purines.

Clinically ineffective *trans* isomer of cisplatin (transplatin) cannot form intrastrand cross-links between adjacent purines for sterical reasons. It has been, therefore, speculated that these DNA adducts of clinically effective cisplatin and its simple analogues are most likely responsible for antitumor activity of these drugs. Nevertheless, the DNA lesion (or lesions) of cisplatin and its simple analogues related to antitumor effect of platinum complexes still remains (or remain) to be established conclusively.

The bifunctional platinum complexes can form DNA interstrand crosslinks, but these lesions are not considered the lesions responsible for antitumor effect. This view is mainly derived from the observation that clinically ineffective transplatin forms more interstrand cross-links than does cisplatin. The latter speculation is, however, based on the assumption that both isomers form identical interstrand DNA lesions. However, DNA interstrand cross-links of transplatin have been studie less thoroughly so that the latter assumption has no experimental support.

A systematic study of the interstrand lesion formed in DNA by clinically ineffective transplatin revealed that this lesion was formed between the sites in DNA, which were different from those involved in the interstrand cross-link of cisplatin. In addition, the DNA interstrand cross-links of cisplatin and transplatin induce in DNA different conformational alterations.

In addition, we have found that the amount of interstrand cross-links formed by cisplatin or transplatin in supercoiled DNA is markedly higher in comparison with the amount of these lesions formed in linear or relaxed DNA. The effect increased with the decreasing level of the platination. Interestingly, the modification of negatively supercoiled DNA corresponding to 1 platinum bound per 5×10^5 nucleotide residues resulted mainly in interstrand cross-links so that this lesion became a major DNA adduct.

Taken together, the results of this work support the view that the role of the DNA interstrand lesions in the mechanism of antitumor effect of platinum drugs is significant, so that it deserves further examinations.

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